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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,656	09/02/2001	Jack Bech Nielsen	5753.204-US	7015

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EXAMINER
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ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 04/11/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/831,656	NIELSEN ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-42* is/are pending in the application.

4a) Of the above claim(s) *38-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 8 is acknowledged. The traversal is on the ground(s) that there is an incorrect factual assessment of the prior art in that the stated reference WO 91/14772 does not teach a maltogenic alpha-amylase. This is not found persuasive because the *Bacillus lichenformis* alpha amylase taught in the reference is known in the art to have useful maltogenic properties as taught by Vickers *et al.*, June 1995, Journal of the Institute of Brewing, Vol. 102, No. 2; pp. 75-78 (see IDS); see entire Abstract and Conclusion; and because the WO 91/14772 reference does teach the usefulness of such sequences in transformed cereal plants.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims a plant cell comprising a gene encoding any maltogenic alpha-amylase; a maltogenic alpha amylase derived from a microorganism; a maltogenic alpha amylase having the amino acid sequence of SEQ ID NO: 2, a maltogenic alpha-amylase having amino acid sequence 1-686 of the amino acid sequence encoded by SEQ ID NO: 1; a maltogenic alpha-amylase having an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 2; and a maltogenic alpha-amylase having an amino acid sequence having at least 70% sequence identity to amino acid sequence 1-686 of the amino acid sequence encoded by SEQ ID NO: 1.

Applicant describes SEQ ID NO: 1 encoding SEQ ID NO: 2, and plant cells and plants transformed therewith.

Applicant does not describe any DNA or amino acid sequences other than SEQ ID NO: 1 and 2 or plant cells and plants transformed therewith.

Given the claim breadth and lack of guidance as discussed above, the specification does not provide an adequate written description of the claimed invention.

See *University of California V. Eli Lilly and Co.,* 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a

recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

Claims 23-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant broadly claims a nucleotide sequence encoding any maltogenic alpha-amylase; a maltogenic alpha amylase derived from a microorganism; a maltogenic alpha amylase having the amino acid sequence of SEQ ID NO: 2, a maltogenic alpha-amylase having amino acid sequence 1-686 of the amino acid sequence encoded by SEQ ID NO: 1; a maltogenic alpha-amylase having an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 2; a maltogenic alpha-amylase having an amino acid sequence having at least 70% sequence identity to amino acid sequence 1-686 encoded by SEQ ID NO: 1; transgenic cereal cells and plants thereof; and seeds comprising said sequences encoding an alpha-amylase in an amount effective to delay staling of bread baked from the seed.

Applicant teaches SEQ ID NO: 1 and 2; hypothetical amino acid substitutions to the polypeptide of SEQ ID NO: 2 from maltogenic alpha amylase variants disclosed in WO 99/43794 (specification pages 6-10); and prophetic biolistic transformation of wheat (Example 1 pages 21-24); and a proposed construction of a construct comprising the 'Novamyl' (SEQ ID NO: 1) maltogenic alpha amylase transformed into wheat protoplast cells and regenerated into mature wheat plants.

Applicant does not teach any cereal cell or cereal plant comprising any of the claimed variants of SEQ ID NO: 1 and 2 or comprising any other maltogenic alpha amylase.

Isolating DNA fragments using stringent hybridization conditions, does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40 :857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65^0C (page 859, left column, 2nd paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2).

Further, the isolation of orthologous DNA sequences from other species introduces an element of unpredictability. The limitation is introduced in finding homologous regions that would adequately enable either PCR amplification or southern hybridization and would entail using either degenerate primers or probes with limited sequence identity. Thus the screen for orthologous sequences would isolate many genes other than those of interest. The inherent unpredictability in isolation of a homologous sequence encoding the same protein activity is illustrated in an example where a small number of changes to the coding region for a strict desaturase resulted in an enzyme with a hydroxylase activity and that a small number of changes to the coding region of a desaturase could account for the functional divergence seen across a

range of enzymes involved in fatty acid metabolism (Broun P. *et al.* Science Vol. 282; 13 November 1998, pp. 1315-1317; Abstract lines 4-6 and p. 1317 column 1, lines 37-56).

Furthermore, the difficulty of predicting enzyme activity based upon sequence identities that vary between 1% to 30% can be extrapolated from the example where a small number of changes have been introduced into proteins that are well characterized with regard to their structure, and the results revealed that the structural determinants were more complex than believed (Guinto, E R. *et al.* PNAS, USA Vol. 96, pp. 1852-1857, March 1999; see Abstract).

Moreover, the production of variants of an alpha amylase of the bacterial strain *Bacillus licheniformis* that would still possess alpha amylase activity cannot be accurately predicted when the detailed descriptions of the electrostatic relationships are insufficient for a rational engineering of enzyme activity. (Nielsen J. *et al.* Protein Engineering, 2001; Vol. 14, No. 7; pp. 505-512; see page 512, first column).

The unpredictability in obtaining a change in phenotype when attempting to modify metabolism in a plant is exemplified by the overexpression in potatoes of an ADPglucose pyrophosphorylase gene from *E. coli* wherein the increased activity resulted in an increased flux into the starch pathway but also resulted in an increase in the capacity of the tubers to degrade the starch in a manner proportionate to the increased flux (Sweetlove L. *et al.,* Biochem J., 1996; Vol. 320; pp. 493-498; see Abstract).

Given the lack of guidance for isolating any maltogenic alpha amylase gene, or for making functional maltogenic alpha amylases with any number of amino acid substitutions; or for making any non-exemplified polynucleotide having 70% sequence identity to SEQ ID NO: 1, the breadth of the claims, and given the unpredictability in the art, undue trail and error

experimentation would be needed by one skilled in the art to isolate a multitude of non-exemplified maltogenic alpha amylase, or to evaluate the ability of a multitude of non-exemplified functional maltogenic variants or non-exemplified polynucleotide sequences having at least 70% sequence identity to alter the delay of staling of bread baked from the seeds of any of the claimed non-exemplified transformed cereal plant species. Therefore, the invention is not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-26, 30, 33 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At Claim 25, lines 2-3, "the amino acid sequence of amino acids 1-686 of SEQ ID NO: 1" is unclear because SEQ ID NO: 1 is a polynucleotide.

At Claim 26, lines 4-5, "the amino acid sequence of amino acids 1-686 of SEQ ID NO: 1" is unclear because SEQ ID NO: 1 is a polynucleotide.

At Claim 33, lines 4 and 6-7, "the amino acid sequence of amino acids 1-686 of SEQ ID NO: 1" is unclear because SEQ ID NO: 1 is a polynucleotide.

At Claim 36, lines 4 and 6-7, "the amino acid sequence of amino acids 1-686 of SEQ ID NO: 1" is unclear because SEQ ID NO: 1 is a polynucleotide.

Claim 30 employs improper Markush terminology in its recitation in line 1 and 2 of "plant cell of Claim 35 and the progeny". Replacement of "and" with --or—in line 1 would obviate this rejection. See MPEP 2173.05(h).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23-24 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Ooyen *et al.*, U.S. Patent 5,705,375 issued January 6, 1998 in light of Vickers *et al.* 1995.

Van Ooyen teaches a maltogenic alpha amylase isolated from isolated *Bacillus lichenformis* (Example 2, columns 10-11) and transformation and regeneration protocols for making transgenic wheat plants comprising a maltogenic alpha amylase (column 7, line 60 to column 8, line 6). The *Bacillus lichenformis* alpha amylase is inherently maltogenic as taught by Vickers *et al.* (see Abstract and Conclusion).

Claims 23-24, 27, 30-32, 34-35, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Barro F. *et al.*, Nature Biotechnology, November 1997; Vol. 15; pp. 1295-1299.

Barro teaches transformation of wheat with constructs comprising HMW subunit genes and endosperm specific promoters (page 1298 column 2), and expression of the HMW gene products in the endosperm of wheat such that the dough made from said transgenic seeds had increased strength (page 1298 column 1). Since Claims 23-24, 27, 30-32, 34-35, and 37 do not teach an isolated or heterologous nucleotide sequence encoding a maltogenic alpha amylase, the claims read upon the endogenous maltogenic alpha amylases and the seeds specific promoters to which they are operably linked, and thus inherently teach a maltogenic alpha amylase in the seeds of any transgenic wheat plant and transgenic cells thereof. Further, the amount effective to delay

staling of bread baked from the seed is also an inherent property of transgenic wheat seeds since the maltogenic properties of the endogenously expressed alpha amylases would bring a delay of staling property to bread made from said seeds. Thus, the reference teaches all the limitations of Claims 23-24, 27, 30-32, 34-35, and 37.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-24, 27-28, 30-32, 34-35, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pen J., WO 91/14772 published October 3, 1991 in view of Barro F. *et al.*, Nature Biotechnology, November 1997; Vol. 15; pp. 1295-1299.

Applicant broadly claims a maltogenic alpha-amylase; a maltogenic alpha amylase derived from a microorganism; a maltogenic alpha amylase having the amino acid sequence of SEQ ID NO: 2, a maltogenic alpha-amylase having amino acid sequence 1-686 of the amino acid sequence encoded by SEQ ID NO: 1; a maltogenic alpha-amylase having an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 2; a maltogenic alpha-amylase having an amino acid sequence having at least 70% sequence identity to amino acid sequence 1-686 encoded by SEQ ID NO: 1; transgenic cereal cells and plants thereof; and seeds comprising said sequences encoding an alpha-amylase in an amount effective to delay staling of bread baked from the seed.

Pen teaches expression of a maltogenic alpha amylase gene product at commercially acceptable levels in seeds of tobacco transformed with a cDNA encoding the alpha amylase from *Bacillus licheniformis* (Example 16 pages 37-38) and suggests incorporation of said invention into seeds of such plants as wheat (page 9 lines 17-26).

Pen does not teach transformation of wheat with endosperm specific promoters and expression of a transgene in wheat seed.

The teachings of Barro are discussed supra.

It would have been obvious at the time of Applicant's invention to modify the invention of Pen to substitute the transformed wheat comprising endosperm specific promoters of Barro. One of skill in the art would have been motivated by the knowledge common in the art that polynucleotides encoding maltogenic alpha amylases are valuable materials for engineering the carbohydrate of seeds of plants by genetic engineering as taught by Pen, and the success of Barro in expressing a transgene in the seeds of a wheat plant such that the dough from said wheat seeds was altered, and that one would have had a reasonable expectation of success of expressing genes in transformed plants, plant cells and seeds.

Claims 23-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pen J., WO 91/14772 published October 3, 1991 in view of Barro F. *et al.*, Nature Biotechnology, November 1997; Vol. 15; pp. 1295-1299 and in further view of Accession number P19531 submitted February 1, 1991, Diderichesen *et al.* and Christophersen *et al.*

Applicant broadly claims a maltogenic alpha-amylase; a maltogenic alpha amylase derived from a microorganism; a maltogenic alpha amylase having the amino acid sequence of SEQ ID NO: 2, a maltogenic alpha-amylase having amino acid sequence 1-686 of the amino acid

sequence encoded by SEQ ID NO: 1; a maltogenic alpha-amylase having an amino acid sequence having at least 70% sequence identity to SEQ ID NO: 2; a maltogenic alpha-amylase having an amino acid sequence having at least 70% sequence identity to amino acid sequence 1-686 encoded by SEQ ID NO: 1; transgenic cereal cells and plants thereof; and seeds comprising said sequences encoding an alpha-amylase in an amount effective to delay staling of bread baked from the seed.

The teachings of Pen and Barro are discussed supra.

Pen and Barro do not teach a maltogenic alpha amylase having at least 70% sequence identity to SEQ ID NO: 2 or 70% sequence identity to the amino acid sequence encoded by the nucleic acid set forth in SEQ ID NO: 1 isolated from the *Bacillus* strain NCIB 11837.

Diderichesen teaches a maltogenic alpha amylase having at least 70% sequence identity to SEQ ID NO: 2 or 70% sequence identity to the amino acid sequence encoded by the nucleic acid set forth in SEQ ID NO: 1 isolated from the *Bacillus* strain NCIB 11837; see GenBank Accession number P19531 in view of Christopherson C. *et al.* Starch/Starke vol. 50, 1998; No. 1 (see IDS, paper number 3); pp. 39-45; see bibliographic reference number 5. Although the sequence report does not show 100% sequence identity between the GenBank sequence and the sequence of the claimed invention, the Christopherson and Diderichesen references teach that the two different reported amino acid sequences for the enzyme encoded by the alpha amylase gene, both of which are isolated from *Bacillus* strain NCIB 11837, are one and the same. Thus, the reference teaches 100% sequence identity to SEQ ID NO: 2.

It would have been obvious at the time of Applicant's invention to modify the invention of Pen to substitute the transformed wheat comprising endosperm specific promoters of Barro. One of skill in the art would have been motivated by the knowledge common in the art that polynucleotides encoding maltogenic alpha amylases are valuable materials for engineering the carbohydrate of seeds of plants by genetic engineering as taught by Pen, and the success of Barro in expressing a transgene in the seeds of a wheat plant such that the dough from said wheat seeds was altered, and that one would have had a reasonable expectation of success of expressing genes in transformed plants, plant cells and seeds. The expression of the maltogenic alpha amylase at levels sufficient to delay staling would have been inherent or the optimization of process parameters.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the receptionist, whose telephone number is (703) 308-0196.

Russell Kallis Ph.D.
March 28, 2003

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638